REMARKS/ARGUMENTS

Applicants have amended the specification under 37 C.F.R. § 1.121 to remove a "SEQ ID NO:" that does not have a respective sequence in the Sequence Listing submitted herewith. Applicants assert that one of ordinary skill in the art would be able to locate the strain having the mutation that was erroneously labeled with a "SEQ ID NO:" using the instant disclosure (see, paragraph 155 of the specification). By way of this error, paragraph 91 was amended to maintain a numerical order to the sequences identified in the specification. The Sequence Listing submitted herewith reflects these amendments. Applicants have included a marked up version of the paragraphs as amended herein as Appendix A. For the convenience of the Examiner, Applicants have included a clean copy of the paragraphs as amended herein as Appendix B. Applicants assert that no new matter has been added.

CONCLUSION

Applicants have amended the specification to correct a sequence error. The amended specification is consistent with the Sequence Listing that is submitted herewith. Therefore, these amendments do not narrow the scope of the claims within the meaning of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 586, 56 USPQ2d 1865, 1886 (Fed. Cir. 2000).

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Respectfully submitted,

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Appendix A

Version With Markings to Show Changes Made

Paragraph 155 (once amended):

In a specific embodiment, at least one *ERG9* (squalene synthase) (GenBank Accession No. X59959; SEQ ID NO:409) modification is generated by standard means in the art to create a "bottleneck" in the pathway, thereby permitting the shuttling of increased amounts of FPP to the bioengineered diterpene pathway. One means to partially block a transformation is achieved by employing a temperature-sensitive mutation which allows examination of impaired enzymatic activity without the adverse effect of completely blocking metabolism. Temperature-sensitive mutations weaken an enzyme's secondary structure. The resultant protein becomes especially sensitive to thermal denaturation, thereby rendering its activity temperature-sensitive. A temperature-sensitive ERG9 mutation (Karst *et al.*, 1971) was incorporated by genetic cross into the yeast comprising a chromosomal nucleic acid sequence encoding a GGPP synthase under the control of an inducible promoter. A strain comprising the *erg9-1* [(SEQ ID NO:413)] temperature-sensitive mutation was purchased from American Type Culture Collection (ATCC 64031) and tetrads from the genetic crosses were selected by observing growth rate at various temperatures as compared to the control strain EHY1.

Paragraph 91 (once amended):

The representative example employed herein was a sterol uptake control mutant (*upc*$^-$) that was isolated *via* ethylmethanesulfonate mutagenesis from wild-type *Saccharomyces cerevisiae* (Lewis *et al.*, 1998). The sterol uptake control *UPC2* allele *upc2-1* (SEQ ID NO:399) increases the metabolic flux of sterol biosynthesis. It was originally cloned by calcium sensitivity, and the protein contains a DNA binding motif. The *upc2-1* allele confers Erg$^-$ Hem$^+$ prototrophy and is a semi-dominant mutation. The mutation is a point mutation that results in an Asp residue instead of a Gly residue at amino acid 888. The *upc2-1* allele (Crowley *et al.*, 1998; Leak *et al.*, 1999; both incorporated by reference in their entirety herein) is utilized in the compositions and methods of the present invention for both overcoming control of sterol importation uptake and increasing sterol biosynthesis

(increasing metabolic flux). Another example of a gene that confers such activity is SUT 1 (SEQ ID NO:[414] 413; Karst et al., 2001). In another specific embodiment, two separate alleles which confer both phenotypes, or a different single allele which confers both phenotypes, are utilized *in lieu* of the *upc2-1* allele.

Appendix B

Clean copy of Specification as Amended April 15, 2002

Paragraph 91 (once amended):

The representative example employed herein was a sterol uptake control mutant (*upc*$^-$) that was isolated *via* ethylmethanesulfonate mutagenesis from wild-type *Saccharomyces cerevisiae* (Lewis *et al.*, 1998). The sterol uptake control *UPC2* allele *upc2-1* (SEQ ID NO:399) increases the metabolic flux of sterol biosynthesis. It was originally cloned by calcium sensitivity, and the protein contains a DNA binding motif. The *upc2-1* allele confers Erg$^-$ Hem$^+$ prototrophy and is a semi-dominant mutation. The mutation is a point mutation that results in an Asp residue instead of a Gly residue at amino acid 888. The *upc2-1* allele (Crowley *et al.*, 1998; Leak *et al.*, 1999; both incorporated by reference in their entirety herein) is utilized in the compositions and methods of the present invention for both overcoming control of sterol importation uptake and increasing sterol biosynthesis (increasing metabolic flux). Another example of a gene that confers such activity is SUT 1 (SEQ ID NO:413; Karst et al., 2001). In another specific embodiment, two separate alleles which confer both phenotypes, or a different single allele which confers both phenotypes, are utilized *in lieu* of the *upc2-1* allele.

Paragraph 155 (once amended):

In a specific embodiment, at least one *ERG9* (squalene synthase) (GenBank Accession No. X59959; SEQ ID NO:409) modification is generated by standard means in the art to create a "bottleneck" in the pathway, thereby permitting the shuttling of increased amounts of FPP to the bioengineered diterpene pathway. One means to partially block a transformation is achieved by employing a temperature-sensitive mutation which allows examination of impaired enzymatic activity without the adverse effect of completely blocking metabolism. Temperature-sensitive mutations weaken an enzyme's secondary structure. The resultant protein becomes especially sensitive to thermal denaturation, thereby rendering its activity temperature-sensitive. A temperature-sensitive ERG9 mutation (Karst *et al.*, 1971) was incorporated by genetic cross into the yeast comprising a chromosomal nucleic acid sequence encoding a GGPP synthase under the control of an inducible promoter. A strain comprising the *erg9-1* temperature-sensitive mutation was purchased from American Type

Culture Collection (ATCC 64031) and tetrads from the genetic crosses were selected by observing growth rate at various temperatures as compared to the control strain EHY1.